Use of human iPSC-derived neurons from Huntington's Disease patients to develop novel, disease-modifying small molecule structural corrector drug candidates targeting the unique, neurotoxic conformation of mutant huntingtin

Grant Award Details

Use of human iPSC-derived neurons from Huntington's Disease patients to develop novel, disease-modifying small molecule structural corrector drug candidates targeting the unique, neurotoxic conformation of mutant huntingtin

Grant Type: Early Translational IV

Grant Number: TR4-06847

Project Objective: The project objective of this DCF award is to identify new small molecule hits that mitigate the neurotoxicity of mutant huntingtin (mHtt) and, from these hits, early lead candidates via iterative in vitro and in silico screening. At the end of the project the PI expects to have identified four compounds, from two series, that have potent activity in two in vitro assays and are orally bioavailable and centrally penetrant in mice.

Investigator:

Name:	John Griffin
Institution:	Numerate, Inc.
Type:	PI

Disease Focus: Huntington's Disease, Neurological Disorders

Human Stem Cell Use: iPS Cell

Award Value: $520,015

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Grant Application Details

Application Title: Use of human iPSC-derived neurons from Huntington's Disease patients to develop novel, disease-modifying small molecule structural corrector drug candidates targeting the unique, neurotoxic conformation of mutant huntingtin

Public Abstract:	The long-term objective of this project is to develop a drug to treat Huntington's disease (HD), the most common inherited neurodegenerative disorder. Characterized by involuntary movements, personality changes and dementia, HD is a devastatingly progressive disease that results in death 10–20 years after disease onset and diagnosis. No therapy presently exists for HD; therefore, this project is highly innovative and ultimately aims to deliver something transformative for the HD patient population. The specific goal of the proposed research will be to achieve preclinical proof-of-concept with a novel small molecule that binds to and ameliorates the neurotoxicity of the mutant huntingtin (mHtt) protein that causes HD. Rationale for development of such compounds comes from previous research that found that mHtt assumes a shape that is selectively toxic to neurons, and that small molecules that disrupt this shape can reduce mHtt's toxicity in primary neurons. Critical to the proposed studies will be assays that employ human striatal neurons derived from adult and juvenile HD patients and generated with induced pluripotent stem cell (iPSC) technology. These HD i-neurons display many characteristics that are also observed in striatal neurons of HD patients, including reduced survival times. They provide the most genetically precise preclinical system available to test for both drug efficacy and safety.
Statement of Benefit to California:	The long-term objective of this project is to develop a first-in-class, disease-modifying drug to treat Huntington's disease (HD), a devastatingly progressive genetic disorder that results in death 10–20 years after disease onset and diagnosis. No therapy presently exists for HD; therefore, this highly innovative project aims to deliver a medical breakthrough that will provide significant benefit for California's estimated > 2000 HD patients and the family members, friends and medical system that care for them. The proposed research will be performed at a biotechnology startup, a leading academic research center and two contract research organizations, all of which are California-based. The work will over time involve more than 10 California scientists, thereby helping to employ tax-paying citizens and maintain the State's advanced technical base. Finally, an effective, proprietary drug for the treatment of HD is expected to be highly valuable and to attract favorable financial terms upon out-licensing for development and commercialization. These revenues would flow to the California companies and institutions (including CIRM) that would have a stake in the proceeds.